teaches the use of recombinant vaccinia virus- or baculovirus-vector vaccines, expressing the entire or portions of the M segment. The Examiner states:

> The results demonstrate that when hamsters were immunized with a baculovirus recombinant expressing the complete M segment (both the G1 and G2 proteins) 9/9 hamsters immunized once and 4/4 immunized twice were protecte from later challenge. Further, incomplete protection was observed using vaccinia recombinants expressing only G1 or only G2 and no protection was observed using vaccinia/S segment recombinants. Chu et al. provide similar results which teaches that a vaccinia virus-vectored vaccine expressing the M and S segments of Hantaan (HTN) virus could elicit a protective immune response against other hantaviruses, including other Hantaan and Seoul viruses, but not Puumala virus."

First, it is noted that the baculovirus results of Schmaljohn are not pertinent to our DNA vaccines, compositions and methods of use. Baculovirus derived products are produced in insect cells, purified then delivered with adjuvant to an animal. The delivery of a protein immunogen is not analogous to an immunogen that is produced inside a host cell, as it is with DNA delivery. Different types of immune responses are elicited by protein that is injected versus protein synthesized within the host. Therefore, someone having ordinary skill in this art would not find our DNA vaccines and immunogenic compositions obvious from, or even particularly relevant to, Schmaljohn's baculovirus-derived protein experiments and data.

Second, the Examiner's statement on page 6 of the Office Action is incorrect:

> "In summary, Schmaljohn, Chu et al. and Arikawa et al. provide detailed guidance for the effectiveness of specific DNA vaccines for Hantaan virus. Further Schmaljohn and Arikawa et al specifically teach that alternative vaccine strategies are sought that further development of the DNA Hantaan virus vaccine would [be] necessary."

Schmaljohn and Chu do not teach DNA vaccines, but rather recombinant vaccinia virus vaccines—which are not the same as DNA vaccines. Although vaccinia vaccines are closer to DNA vaccines than are baculovirus-derived vaccines, there are key differences which make it quite unreasonable—if not impossible—to infer that a vaccinia vaccine (either successful or not successful) such as allegedly disclosed by Schmaljohn or Chu (or generally mentioned by Arikawa) will predict if a DNA vaccine composition will work. For instance, two such differences are:

(1) Vaccinia is a live virus and is used to infect host cells. Immune responses to vaccinia virus are greater than the responses to the foreign gene expression product that the vaccinia virus produces. Because vaccinia virus stimulates strong cell-mediated immune responses, whereas Hantaan virus does not, the type of immune response generated is different than is elicited by a DNA vaccine. Thus, one would not use vaccinia vaccine technology as taught by Schmaljohn, Chu or Arikawa in combination with Montgomery or Donnelly to achieve our claimed DNA vaccine compositions.

(2) Vaccinia virus replicates only in the cytoplasm, and uses viral enzymes, not host cell enzymes, to copy its DNA genome. In contrast, DNA vaccines are transported to the nucleus and use host cell enzymes to copy the plasmid DNA. It can not be reasonably predicted from a vaccinia virus vaccine if the plasmid DNA encoding the same gene sequences will be copied successfully. RNA viruses, such as Hantaan virus, do not normally enter host cell nuclei; consequently, they may contain sequences that encode splice sites. Such sites would render the transcript inoperable. Therefore, the vaccinia virus vaccine allegedly taught by Schmaljohn and Chu (and generally mentioned by Arikawa) would not have been reasonably predictive of whether or not a DNA vaccine composition would work.

In other words, in view of (1) and (2) alone, the disclosures of Schmaljohn, Chu and Arikawa would not have lead someone to combine these references with Montgomery and Donnelly to arrive at the DNA vaccine compositions of our invention. And regarding Arikawa in particular, this reference has nothing at all to do with DNA vaccines, or really any vaccines. From the Examiner's comments on this reference, we assume that the Examiner is relying on Arikawa's general statement at the end of the reference to support the contention that DNA Hantaan virus vaccines are desirable and acheivable. However, Arikawa merely indicates that the results therein would help in the rational design of "recombinant DNA vaccines". This is non-instructive with regard to a practical DNA vaccine approach, and would not make up for the deficiencies of either Schmaljohn or Chu.

In addition, another reason that the vaccinia vaccine would not predict efficacy comes from data comparing the two vaccines in monkeys. The Hantaan DNA vaccine

elicits high levels of long lasting neutralizing antibodies, whereas the vaccinia Hantaan vaccine elicits low levels of short-lived neutralizing antibodies. As someone having ordinary skill in this would readily understand, this is indicative that the DNA vaccine and the vaccinia vaccine have different immune responses, and utilize different mechanisms. One would not render obvious the other.

Therefore, we submit that none of claims 28-32, 35-42, 44, 45, 48 and 49 would have been obvious at the time of our invention, in light of the five references cited by the Examiner. Reconsideration and withdrawal of this rejection is requested.

Having addressed all of the Examiner's outstanding concerns, it is believed that this application is in condition for allowance, and notice of such is earnestly solicited.

By: _____

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